CEREBRAL TOXOPLASMOSIS

Introduction

- Toxoplasmosis is caused by infection with the obligate intracellular parasite Toxoplasma gondii.

- **Cats** are the definitive **host** for this organism

- Acute toxoplasmosis infection is **asymptomatic** in most **immune-competent** individuals.

Transmission

Mode of transmission	
Oral	Transmission can be attributed to eating raw /undercooked meat or contaminated vegetables or fruits.
Transplacental	About 1/3 of all women who acquire infection with T. gondii during pregnancy transmit the parasite to the fetus; the remainder give birth to normal, uninfected babies. Recrudescent maternal infection does not cause congenital disease. Thus, women who are seropositive before pregnancy usually are protected against acute infection and do not give birth to congenitally infected neonates.
Transmission via blood and organs	Direct transmission of the parasite by blood or organ products during transplantation takes place at a low rate. Viable parasites can be cultured from refrigerated anticoagulated blood, which may be a source of infection in individuals receiving blood transfusions. T. gondii infection also has been reported in kidney

Transmission

- Humans can catch this disease from:
  - Coming into contact with infected cat feces
  - Eating raw or undercooked meat that’s infected
  - Eating contaminated vegetables or fruits
  - Congenital transmission - transmission from a mother with acute toxoplasma infection to her foetus.

- **NB:** Once a person is infected, the infection remains in the body for life, usually in an **inactive form**. It can **reactivate when that person’s immune system is weak**.

Congenital toxoplasmosis

- **Congenital toxoplasmosis** is an infection of newborns that results from the **transplacental passage** of parasites from an infected mother to the fetus.

- These infants usually are asymptomatic at birth but later manifest a wide range of signs and symptoms, including:
  - Chorioretinitis,
  - Strabismus,
  - Epilepsy,
  - Psychomotor retardation.

Congenital toxoplasmosis: Effect of gestational age on fetal outcomes

- Of the various factors that influence fetal outcome, gestational age at the time of infection is the most critical
  - There is essentially **no risk** if the mother becomes infected **6 months *before conception***.
  - If infection is acquired **<6 months before conception**, the **likelihood of transplacental infection increases** as the interval between infection and conception decreases.
  - In pregnancy, if the mother becomes infected during the **first trimester**, the incidence of **transplacental infection is lowest** (~15%), but the **disease in the neonate is most severe**.
  - If maternal infection occurs during the **third trimester**, the incidence of **transplacental infection is greatest** (65%), but the **infant is usually asymptomatic at birth**.

Congenital toxoplasmosis: Effects on mother and infants

- Infected infants who are normal at birth may have a higher incidence of **learning disabilities** and **chronic neurologic sequelae** than uninfected children.

- Only a small proportion (20%) of women infected with T. gondii develop clinical signs of infection.

- Often the diagnosis is first appreciated when routine postconception serologic tests show evidence of specific antibody.

Toxoplasmosis as an opportunistic infection

- In the immunocompetent host, both the humoral and the cellular immune responses control infection;
  - These include induction of parasiticidal antibody, activation of macrophages, production of interferon (IFN-γ), and stimulation of cytotoxic T lymphocytes of the CD8+ phenotype.
  - These antigen-specific lymphocytes are capable of killing both extracellular parasites and target cells infected with parasites.
- As the parasites are cleared from the acutely infected host, tissue cysts begin to appear, usually within the CNS and the retina.

Toxoplasmosis as an opportunistic infection (cont'd)

- In the immunocompromised or fetal host, the immune factors necessary to control the spread of the parasite are lacking.
  - This altered immune state allows the persistence of the parasite and gives rise to progressive focal destruction that results in organ failure (i.e., necrotizing encephalitis, pneumonia and myocarditis).
- Persistence of infection with cysts is common in the immunocompetent host.
  - This **lifelong infection** usually remains **subclinical**.
  - Although the parasites are in a slow metabolic phase, cysts degenerate and rupture within the CNS.
  - This degenerative process, with the development of new cysts, is the most probable source of recrudescent infection in immunocompromised individuals and the most likely stimulus for the persistence of antibody titres in the immunocompetent host.

Clinical manifestations:Immunocompetent hosts

- In persons whose **immune systems** are **intact**, acute toxoplasmosis is usually **asymptomatic** and **self-limited**.
  - The most common manifestation of acute toxoplasmosis is **cervical lymphadenopathy**.
  - Some patients may experience headache, malaise, fatigue, and fever [usually with a temperature of <40°C)
  - Symptoms associated with acute infection usually resolve within several weeks, although the lymphadenopathy may persist for some months.

- In children and adults, chronic infection can persist throughout life, with little consequence to the immunocompetent host.

Clinical manifestations: Congenital toxoplasmosis

- The wide range of clinical manifestations in congenitally infected children includes severe neurologic complications such as:
  - Hydrocephalus,
  - Microcephaly,
  - Mental retardation, and
  - Chorioretinitis

- If prenatal infection is severe, multi-organ failure and subsequent intra-uterine foetal death can occur.

Toxoplasmosis in immunocompromised patients

- Patients with AIDS and those receiving immunosuppressive therapy for lymphoproliferative disorders are at greatest risk for developing acute toxoplasmosis.

- The infection may be due either to reactivation of latent infection or to acquisition of parasites from exogenous sources such as blood or transplanted organs.
- In individuals with AIDS, **>95% of cases** of TE are believed to be due to **recrudescent infection**.
  - In most of these cases, encephalitis develops when the **CD4+ T cell count falls below 100/L**.
  - In immunocompromised hosts, the disease may be **rapidly fatal** if untreated.
- The **signs and symptoms** of acute toxoplasmosis in immunocompromised patients **principally involve the CNS.**

- Later, confusion and drowsiness, seizures, focal weakness, and language disturbances may occur.

- Without treatment, progression to coma occurs in days to weeks.

Cerebral toxoplasmosis: Signs and symptoms

- Sub-acute onset headache
- Fever
- Altered mental status (confusion and drowsiness, impaired consciousness, language disturbances)
- Seizures
- Focal neurological deficits (hemiparesis, hemianopia, aphasia, ataxia, and cranial nerve palsies may be found).
- CD4 usually < 100 cells/mm3. The greatest risk of disease is in those with CD4 < 50 cells/mm3 while clinical disease is rare in patients with CD4 count > 200 cells/mm3.

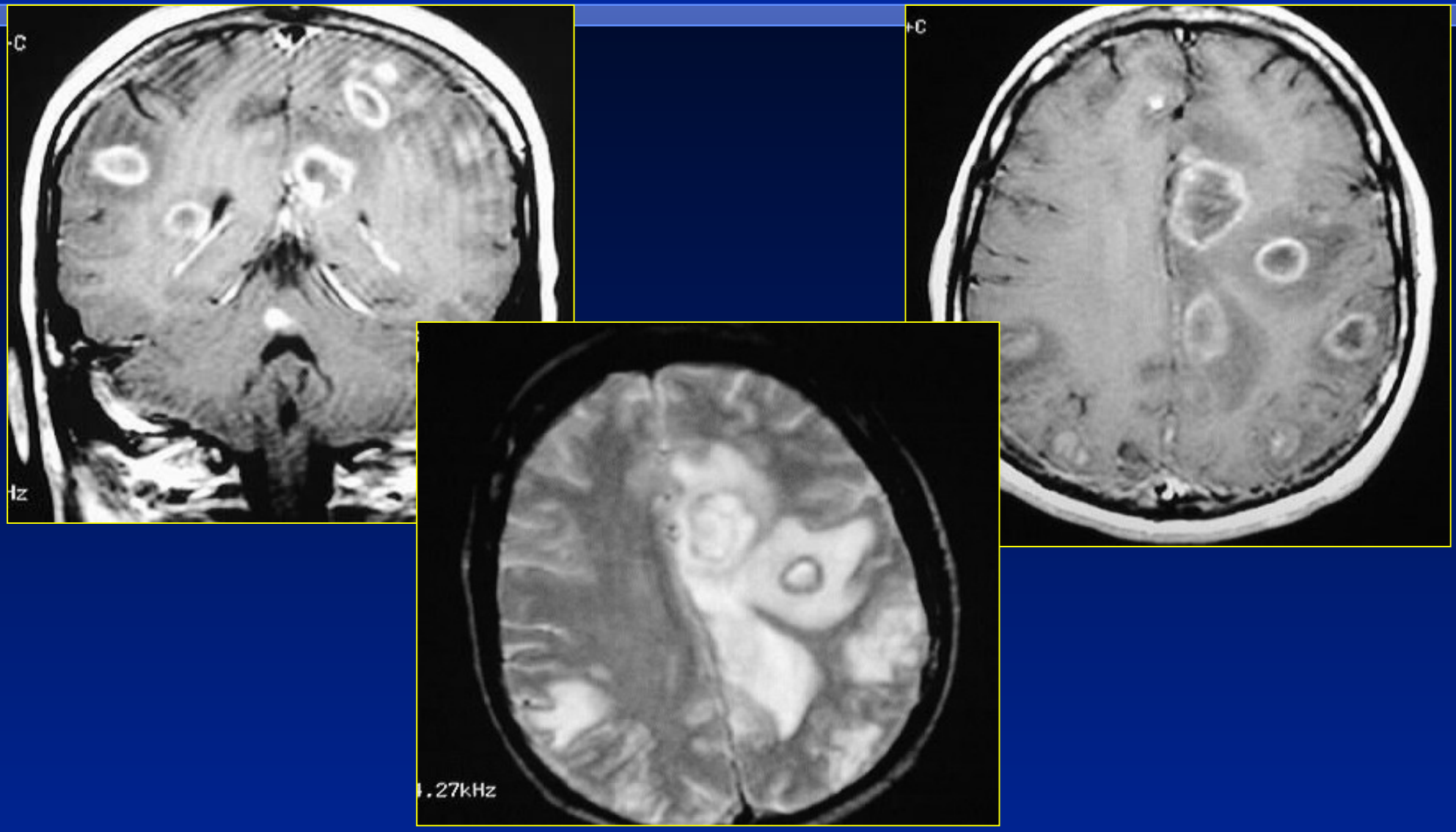
Diagnosis: Presumptive diagnosis

- A presumptive diagnosis of toxoplasma encephalitis is based on the **clinical presentation, serological tests and radiographic evaluation.**
  - The clinical signs and symptoms of toxoplasma encephalitis can be either focal (indicating a specific region of the brain that is infected or inflamed) or generalized (indicating diffuse inflammation of the brain).
  - Toxoplasma encephalitis usually occurs in patients with **CD4+ counts of <100**.
  - Therefore a presumptive diagnosis of cerebral toxoplasmosis should be considered in **patients with CD4 < 100 cells/mm3 with headache, fever, seizures, altered mental status and focal neurological deficit.**

Diagnosis: Serological tests and Imaging

- Toxoplasma antibodies-A **rising anti-toxoplasma IgG** serology in patients with signs and symptoms of toxoplasmosis is useful to support the diagnosis.

- Patients with toxoplasmosis have **single or multiple ring enhancing lesions** on brain CT or MRI scan.



Toxoplasmosis

Differential diagnosis

- Due to the nonspecific diagnosis of toxoplasma encephalitis, a high index of suspicion for other causes of encephalitis such as CNS lymphoma or TB should be maintained throughout the treatment period for presumed toxoplasma encephalitis.

Treatment

- Therapy for toxoplasmosis can be categorized into:
  - Primary prophylaxis,
  - Treatment of acute disease,
  - Secondary prophylaxis.

Treatment: Primary prophylaxis

- Primary prophylaxis is currently recommended in all **HIV-infected patients.**

- Many of the agents used to prevent PJP have activity against T. gondii and afford protection: **TMP-SMX (co-trimoxazole)**, pyrimethamine-sulfadiazine, dapsone-pyrimethamine, and atovaquone with or without pyrimethamine are effective as primary prophylaxis for T. gondii.
  - All PLHIV should receive lifelong cotrimoxazole preventive therapy (CPT) unless they have an allergy to sulfa drugs or develop toxicity from CPT.
  - For HIV exposed and infected infants, CPT should start at 6 weeks of age.
  - **CPT is effective in preventing specific OIs for patients with low CD4 counts (PJP and toxoplasmosis), as well as reducing the risk of common bacterial infections, sepsis, diarrheal illness and malaria.**
  - During pregnancy, CPT should be initiated irrespective of the gestational age and should continue throughout pregnancy, breastfeeding, and thereafter for life. Additional intermittent preventive therapy (sulfadoxine-pyrimethamine (SP)) for malaria is not required in women already on CPT.

- *The increased use of CPT has significantly decreased the incidence of Toxoplasma encephalitis.*

Treatment: Acute toxoplasmosis

- The preferred regimen is:
  - Pyrimethamine 200 mg loading dose, then 50 mg –75 mg/day +Sulfadiazine 1000 mg- 1500mg P.O. 6 hourly + Folinic acid (leucovorin) 10-20mg/day PO
  - Folinic acid is used to reduce ***pyrimethamine-associated haematological toxicity***
- ***NB:*** Folate is not a substitute for folinic acid.

Treatment of acute toxoplasmosis: Alternative regimens

- **Cotrimoxazole**: 5mg/kg of Trimethoprim or 25mg/kg of CTX BD per day for **6 weeks**
  - **NB:** This is the regimen of first choice in Kenya in the absence of key constituents of the preferred first line treatment.
  - An advantage of this regimen over the above one is that it can also be given IV in patients unable to take oral treatment.
- Pyrimethamine plus leucovorin with clindamycin 600 to 900 mg IV Q 6 to 8 hours or 300 to 450 mg orally Q 6 hours for at least 6 weeks.

Comparative efficacy and safety of the sulfadiazine vs clindamycin-based regimens

- Although both regimens are effective, **pyrimethamine-sulfadiazine has been found to be superior to pyrimethamine-clindamycin.**
  - The **risk of progression of toxoplasma encephalitis** has been found to be higher for patients who received pyrimethamine-clindamycin therapy.
  - Furthermore, the **rate of relapse** is **twice as high** in the pyrimethamine-clindamycin group.
- The rate of side effects is similar with both regimens.

- However , pyrimethamine-clindamycin led to fewer discontinuations than pyrimethamine-sulfadiazine.

Sulfadiazine toxicity

- As with other sulfonamides in HIV patients, rashes commonly occur with sulfadiazine therapy.

- Similar to TMP-SMX, various desensitization regimens have been recommended
  - However, it may be simpler to use alternative regimens.

- Renal function should be monitored throughout therapy.
  - Elevated serum creatinine (SrCr) levels, haematuria or decreased urine output may occur secondary to sulfadiazine-induced crystalluria.
  - The water solubility of sulfadiazine is less than that of other sulfonamides;
    - Therefore, hydration (2–3 L/day) is needed to prevent crystalline nephropathy, and aggressive hydration and alkalinization can be used in cases of crystal formation.

Pyrimethamine toxicity

- Pyrimethamine can suppress bone marrow function;
- Thus, concomitant therapy with other medications that suppress marrow function (e.g., AZT or ganciclovir) may not be tolerated.
  - Leucovorin (10–20 mg/day) is always given in conjunction with pyrimethamine to maintain bone marrow function.
  - Folic acid (not folinic acid) should be avoided because it can be used for growth by protozoal organisms, potentially antagonizing pyrimethamine-sulfadiazine activity.
  - Vitamin preparations containing large quantities of folic acid should be discontinued during therapy for T. gondii.

Treatment: Suppressive therapy (Secondary prophylaxis

- Most antiprotozoal agents **do not eradicate the cyst form** of T. gondii.

- Therefore, patients should receive lifelong suppressive therapy unless immune reconstitution occurs as a consequence of HAART.

- The combination of pyrimethamine (25–75 mg/day) plus sulfadiazine (500–1,000 mg PO QID) plus Leucovorin 5mg/day is very effective.

Treatment: Suppressive therapy (Secondary prophylaxis

- Alternative regimens for secondary prophylaxis include
  - Co-trimoxazole in the standard prophylactic dose of 960mg OD.
  - For patients who cannot tolerate sulfa drugs pyrimethamine plus clindamycin can be used .
  - ***NB: Maintenance therapy for Toxoplasma encephalitis with sulfadiazine-pyrimethamine is more effective than clindamycin-pyrimethamine or pyrimethamine alone.***
  - The use of atovaquone with or without pyrimethamine is also effective as prophylaxis for both toxoplasmosis and PCP.

Discontinuation of maintenance therapy

- If using the sulfadiazine/pyrimethamine maintenance regimen, the drugs should be discontinued if:
  - There is sustained immune reconstitution (CD4 count >200 cells/mm for > 6 months)
  - Initial therapy completed and the patient is asymptomatic.
- ***NB: Co-trimoxazole should be continued indefinitely regardless of immune status of the patient.***

Toxoplasmosis in pregnancy

- The same criteria for diagnosis apply in pregnant women as in other patients.
- Children exposed to active disease in their mothers should be assessed for congenital toxoplasmosis.
- Treatment is the same as in non-pregnant patients.

Prevention of toxoplasma gondii infection

- The two major routes of transmission of Toxoplasma to humans are oral and congenital.
  - *Infected patients* ***need not be isolated*** *from other patients and health care workers*
  - HIV-infected patients should be advised not to eat raw and undercooked meat
  - Patients should wash their hands after touching uncooked meats and soil, and fruits and vegetables must be washed before eating
  - HIV-infected patients should avoid stray cats, keep their cats inside, and change the litter box daily. If no one else is available to change the litter box, patients should wash their hands thoroughly afterward.

THE END.

THANK YOU!